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Address inquiries to
Eastman Organic Chemicals Dept.
Distillation Products Industries
Division of Eastman Kodak Company
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Acetals

By J. A. VAN ALLAN

The increasing interest in acetals both as intermediates in organic syntheses and as compounds having industrial applications, such as solvents, plasticizers, etc., prompts this brief summary of procedures for their production.

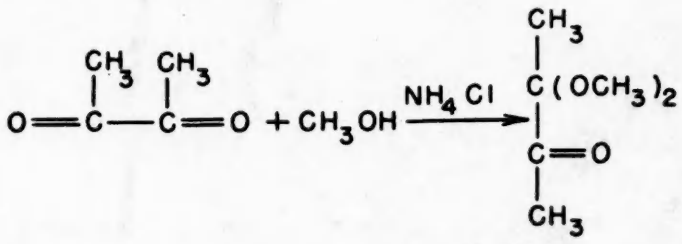
1. *From Aldehydes and Ketones*

A method which has found wide use in the preparation of acetals and ketals is the azeotropic distillation of the water that is formed in acetal formation (1). Glycol and trimethylene glycol react to give cyclic ketals with cyclopentanone, cyclohexanone, biacetyl, benzil, acetophenone, methyl- and phenylglyoxal, and tetralone (2). Ethyl acetoacetate gives particularly good results; the resultant ketal may be saponified with caustic to give the corresponding acid without decarboxylation.

α-Chloroketones, α-bromoketones, α-, β-, γ-, and δ-keto acids, pinacolone, mesityl oxide, and high-molecular-weight ketones are among the wide variety of ketones which form cyclic acetals readily. Besides the usual glycols, nitroglycols, glycerols (3), and sugars have been used. Aldehydes, of course, form cyclic acetals with the same ease. α-Hydroxy acids and ketones form 1,3-dioxolones. Acetals of all the nitro-, methoxy-, and chlorobenzaldehydes and the tolylaldehydes may be prepared by azeotropic distillation of the appropriate aldehyde and alcohol.

A particularly convenient and simple method for the preparation of ketals involves the use of alkyl sulfites as alkylating agents. The aldehyde or ketone and the alkyl sulfite are dissolved in methanol and a few drops of methanolic hydrochloric acid are added as a catalyst. Thus, cyclohexanone gives a 79 percent yield of a dimethyl ketal, benzophenone 95 percent, propionaldehyde 87 percent, etc. (4).

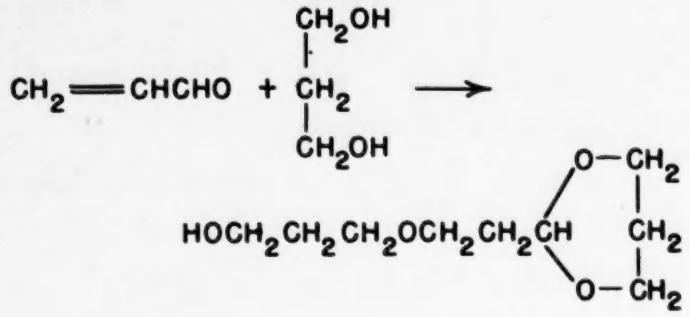
A special case is the reaction of diacetyl with methanol in the presence of ammonium chloride. Only one of the ketone groups is converted to the ketal (5). The yield is 80 percent.



This compound undergoes reactions typical of a ketone with an α-hydrogen atom.

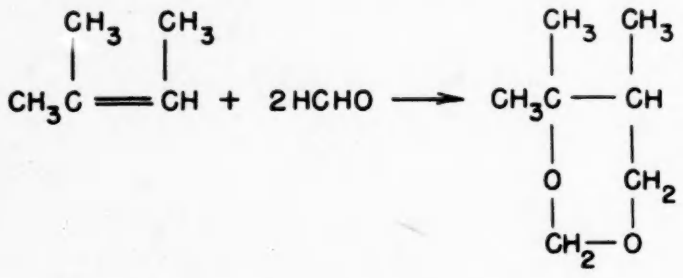
Excellent results have been obtained in the synthesis of acetals from alcohols and aldehydes using the ion-exchange resins. Thus, paraformaldehyde, butanol, and Zeo-Karb-H, under reflux, give a 96 percent yield of the acetal.

If α,β-unsaturated aldehydes and dihydric alcohols are reacted in the presence of an acid catalyst, not only does acetal formation take place but the glycol also adds to the double bond (6). Thus:

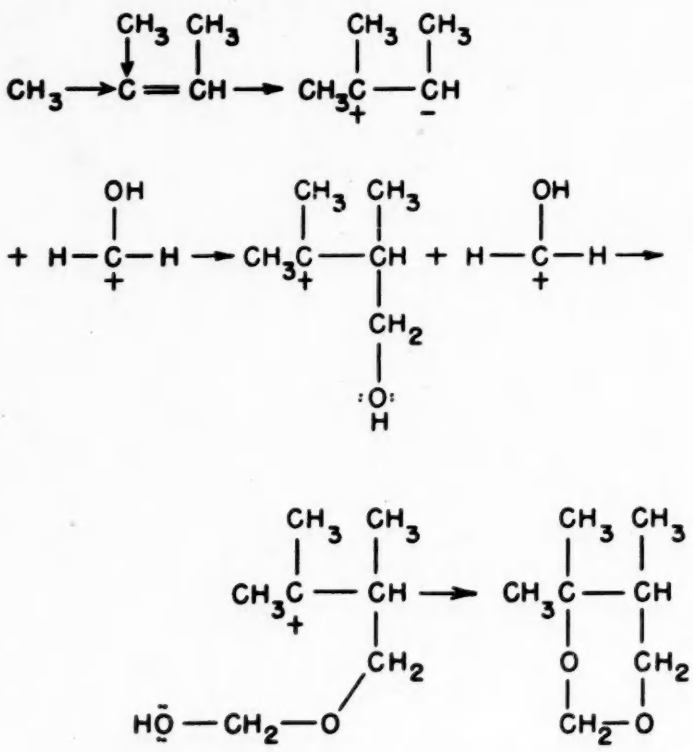


II. *From Olefins*

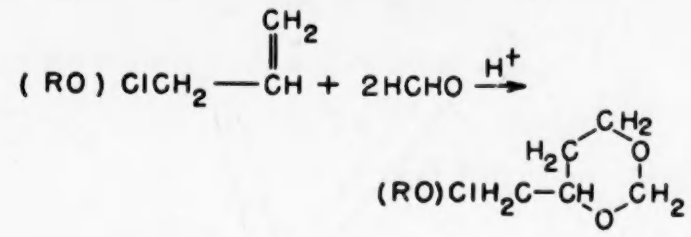
It has been found that during the treatment of aliphatic mono-olefinic hydrocarbons with formaldehyde in the presence of certain acidic catalysts, such as zinc chloride, hydrochloric acid, sulfuric acid, and others, cyclic acetals are formed, according to the following equation (7):



It will be noted that the carbon chain is prolonged, while at the same time a 1,3-dioxane ring is formed. The following mechanism seems quite plausible:



Allyl ethers and chlorides behave in an analogous manner with formaldehyde to yield 4-alkoxymethyl or 4-chloromethyl-1,3-dioxanes. Thus:



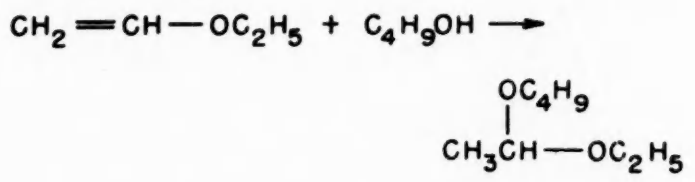
Methallyl chloride, isocrotyl chloride, and acetaldehyde have also been used (8) as well as methallyl cyanide and 2-pentene.

III. *From Acetylene*

Acetylene is a convenient starting material for the production of symmetrical and mixed acetals. Thus, ethylene glycol reacts with acetylene in the presence of a mercuric oxide–boron trifluoride catalyst to produce a cyclic acetal (9). A mechanism is proposed in which the BF_3 is said to be co-ordinated with methanol. This reactive complex then adds to the acetylene to form the acetal. This method is the subject of numerous patents.

IV. *From Vinyl Ethers*

Closely allied with the foregoing synthesis is the formation of acetals from vinyl ethers. In this process, an alcohol and a vinyl ether are mixed in the presence of an acid catalyst. The reaction is spontaneous and exothermic (10):



The vinyl ethers are formed from acetylene and an alcohol over an alkaline catalyst at 120-150 C. Of particular interest are the unsymmetrical acetals which are readily produced by this procedure.

The reaction of butanol with vinyl ethyl ether in the presence of sulfuric acid catalyst produces acetaldehyde ethyl *n*-butyl acetal in 60 percent yield. The same product can be readily obtained by adding ethyl alcohol to vinyl *n*-butyl ether (obtained from sodium *n*-butylate and vinyl chloride or from *n*-butyl α-chloroethyl ether by conversion with sodium alcoholate).

v. *From Vinyl Acetate*

The synthesis of bromoacetaldehyde acetal by brominating vinyl acetate in alcohol at low temperatures has been improved and extended so that 80-90 percent yields of α-bromoacetals are readily obtainable (11).

Acetals are also produced when a vinyl ester and a primary or secondary alcohol are heated together at 25-50 C with a mercury compound and a strongly acidic catalyst. The reaction proceeds in two stages, postulated as

$$RCO_2CH{=}CH_2 + R'OH \longrightarrow RCO_2\overset{CH_2}{\underset{|}{C}}HOR' + R'OH \longrightarrow$$

$$RCOOH + (R'O)_2CHCH_3$$

and mixed acetals can be obtained by adding one mole of one alcohol to the ester–catalyst mixture, followed by the addition of another alcohol. This method is especially useful in preparing ketals.

vi. *From Epoxy Compounds*

Cyclic acetals may be made using epoxy compounds as starting materials. Thus: A mixture of aldehyde and epichlorohydrin, diluted with carbon tetrachloride, is added slowly to greatly diluted stannic chloride in carbon tetrachloride, with stirring, the temperature being kept below room temperature. The reaction is instantaneous. 2-Chloropropylene acetals are thus produced (12).

vii. *From Allyl Chlorides*

Methallyl chloride is treated with an alcohol in the presence of a basic catalyst at 180-200 C to give an acetal (13):

$$CH_2{=}\overset{CH_3}{\underset{|}{C}}H{-}CH_2Cl + ROH \xrightarrow{OH^-}$$

$$CH_3\overset{CH_3}{\underset{|}{C}}H{-}CH(OR)_2$$

The yields are not quoted.

viii. *From Orthoesters*

A review of the reaction of orthoesters with aldehydes has been given recently (14). Yields of about 95 percent have been obtained with aldehydes and ketones using *p*-toluenesulfonic acid as a catalyst.

ix. *From Diphenylketene*

A reaction which does not appear to have been investigated to any extent is the reaction of diphenylketene with ethyl orthoformate to give an acetal (15):

$$(C_6H_5)_2C{=}C{=}O + 2\,HC(OC_2H_5)_3 \longrightarrow$$

$$(C_6H_5)_2C{=}\overset{COOC_2H_5}{\underset{CH(OC_2H_5)_2}{C}}$$

The product is a derivative of the half-aldehyde of malonic acid. Blomquist (16) has recently demonstrated that the ketenes are readily obtainable from aliphatic acids.

x. *From Acetals*

If one heats an acetal having the alkyl group, R′, with another alcohol, R″OH, in the presence of a small amount of acid catalyst, an equilibrium is established in which both possible acetals, together with the mixed acetal, are present:

$$R'{-}CH(OR)_2 + 2\,R''OH \rightleftharpoons$$

$$R'{-}CH(OR'')_2 + 2\,ROH$$

It appears that the acetal with the higher-molecular-alkyl residue predominates. It is apparent that the equilibrium may be shifted to favor the production of acetals with higher molecular weight if the lower-molecular-weight alcohol is removed as formed. Conversely, the production of the lower-molecular-weight acetals is favored by increasing concentration of the lower-molecular-weight alcohol. Polyhydric alcohols react with the simple acetals to give cyclic acetals.

The expansion of this fundamental process forms the subject matter of several patents and papers. Thus, methoxymethoxyethanol is refluxed with methylal in the presence of an acidic catalyst to produce 1,2-bis-(methoxymethoxy)-ethane (17):

$$CH_3OCH_2OCH_2CH_2OH + CH_2(OCH_3)_2 \longrightarrow$$

$$CH_3OCH_2OCH_2CH_2OCH_2OCH_3$$

The initial unsymmetrical acetal, methoxymethoxyethanol, is obtained from 1,3-dioxalane and methanol. In a similar manner, symmetrical acetals react with ethylene chlorohydrins to give chlorinated acetals, which, on treatment with potassium hydroxide, give alkoxymethoxyethanols. Glycolonitrile and methyl formal give methoxymethoxyacetonitrile, while cyanohydrins give mixed formals of the cyanohydrin. It has also been shown that unsymmetrical acetals may be produced from symmetrical acetals and alcohols of the type, XC_2H_4OH, in which X = a hydroxy, alkoxy, or aryloxy group:

$$RCH_2CH(OC_2H_5)_2 + XC_2H_4OH \longrightarrow RCH_2CH(OC_2H_4X)(OC_2H_5)$$

It has been shown that cyclic acetals may be synthesized conveniently from polyhydric alcohols and simple acetals by simply heating the reactants together and removing the lower-boiling alcohol as formed. The method is especially suited to the bromoacetals.

References

(1) Dreyfus, H., Fr. Pat. 745,973 (1933); *Chem. Abstr.*, 27, 4243 (1933).
(2) Böeseken, J., and Tellegen, F., *Reç. trav. chim.*, 57, 133 (1938); *Chem. Abstr.*, 32, 3335 (1938).
(3) Dupire, A., *Comp. rend.*, 214, 359 (1942).
(4) Voss, W., *Ann.*, 485, 283 (1931); *Chem. Abstr.*, 25, 1798 (1931).
(5) Calder, D. S., Fleer, K. B., and Forest Products Chemical Co., U. S. Pat. 2,401,336 (1946); *Chem. Abstr.*, 40, 5069 (1946).
(6) Billig, K., Ger. Pat. 667,793 (1938); *Chem. Abstr.*, 33, 2536 (1939); and Ger. Pat. 696,580 (1940); *Chem. Abstr.*, 35, 6359 (1941).
(7) Farbenindustrie A.-G., I. G., Fr. Pat. 847,255 (1939); *Chem. Abstr.*, 35, 5129 (1941). Fitzky, W., and General Aniline and Film Corp., U. S. Pat. 2,325,760 (1944); *Chem. Abstr.*, 38, 380 (1944).
(8) Standard Oil Development Co., Brit. Pat. 559,041 (1944); *Chem. Abstr.*, 39, 4632 (1945).
(9) Nieuwland, J. A., Vogt, R. R., and Foohey, W. L., *J. Am. Chem. Soc.*, 52, 1018 (1930).
(10) Farbenindustrie A.-G., I. G., Brit. Pat. 352,474 (1930); *Chem. Abstr.*, 26, 5310 (1932).
(11) McElvain, S. M., and Kundiger, D., *Organic Syntheses*, 23, 8 (1943).
(12) Bersin, T., and Willfang, G., *Ber.*, 70, 2167 (1937).
(13) Schmerling, L., Ipatieff, V. N., and Universal Oil Products Co., U. S. Pat. 2,412,012 (1946); *Chem. Abstr.*, 41, 2070 (1947).
(14) Post, H. W., *J. Org. Chem.*, 5, 244 (1940).
(15) Staudinger, H., and Rathsam, G., *Helv. Chim. Acta*, 5, 645 (1922).
(16) Blomquist, A. T., and Spencer, R. D., *J. Am. Chem. Soc.*, 70, 30 (1948).
(17) Sussmann, S., and du Pont de Nemours and Co., Inc., E. I., U. S. Pat. 2,321,557 (1943); *Chem. Abstr.*, 37, 6674 (1943).

Colorimetric Microdetermination of Creatinine and Creatine in Blood and Urine

Stelgens, Wolf, and Schreier (*Z. physiol. Chem.* 286, 218 [1950]) recently described a sensitive and virtually specific method for the determination of micro amounts of creatinine. The method is based on the quantitative reaction between creatinine and a measured excess of potassium mercuric thiocyanate in alkaline solution. After neutralization, the unreacted mercury is extracted with diphenylthiocarbazone (dithizone) and measured colorimetrically, using a photometer and a filter transmitting at 500 mμ. The method covers a range of 0 to 20 micrograms of creatinine and is said to be accurate to ± 5% at the higher levels. Beer's law is obeyed.

Creatine may be present in amounts up to thirty times that of the creatinine without interfering. By application of a preliminary acid treatment, creatine can be converted to creatinine and then measured.

A large number of substances likely to be present in blood and urine were investigated and found to have no effect on the method. However, a cystine concentration of 100 micrograms/ml leads to slightly low results. Samples must be albumin-free. Oxidizing substances which produce a similar yellow color with dithizone can be eliminated by the addition of hydroxylamine hydrochloride.